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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,303	04/09/2004	Rino Rappuoli	20480.019	3584

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EXAMINER
PENG, BO

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,303	RAPPUOLI ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/14/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,22,23,25-28,94-98,114,115,117 and 121-126* is/are pending in the application.

4a) Of the above claim(s) *121 and 123-126* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,22,23,25-28,94-98,114,115,117 and 122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction election

1. Applicants' election of Group I (Claims 94-98), species of SARS virus Spike (S) polypeptide SEQ ID NO: 6042, second S1 peptide SEQ ID NO: 7307, and adjuvant MF59 in the filed on May 14, 2008, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Accordingly, Claims 1-8, 22, 23, 25-28, 94-98, 114, 115, 117 and 121-126 are pending. Claims 121 and 123-126 are withdrawn as non-elected. Claims 1-8, 22, 23, 25-28, 94-98, 114, 115, 117 and 122 are considered in this office action. Claims are examined to the extent of the elected S polypeptide SEQ ID NO: 6042, and second S1 fragment SEQ ID NO: 7307, and adjuvant MF59.

Priority

3. This application claims benefit of the following provisional applications:

60/462,218 filed on 04/10/2003,
60/462,465 filed on 04/11/2003,
60/462,418 filed on 04/12/2003,
60/462,748 filed on 04/13/2003,
60/463,109 filed on 04/14/2003,
60/463,460 filed on 04/15/2003,
60/463,668 filed on 04/16/2003,
60/463,983 filed on 04/17/2003,
60/463,971 filed on 04/18/2003,
60/464,899 filed on 04/22/2003,
60/464,838 filed on 04/22/2003,
60/465,273 filed on 04/23/2003,
60/465,535 filed on 04/24/2003,
60/468,312 filed on 05/05/2003,
60/473,144 filed on 05/22/2003,

60/495,024 filed on 08/14/2003,
60/505,652 filed on 09/23/2003,
60/510,781 filed on 10/11/2003,
60/529,464 filed on 12/11/2003,
60/536,177 filed on 01/12/2004, and
60/560,757 filed on 04/07/2004.

A review of the priority documents shows support for SARS virus Spike (S) polypeptide SEQ ID NOs: 6042 and S1 peptide SEQ ID NO:7307 in the disclosure of 60/510,781 filed on 10/11/2003, 60/510,781 filed on 10/11/2003, 60/529,464 filed on 12/11/2003, 60/536,177 filed on 01/12/2004, and 60/560,757 filed on 04/07/2004. Therefore, the effective filing date for Claims 94-98 has been currently determined to be October 11, 2003, the filing date of 60/510,781.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See Paragraphs [0004]-[0006], [0148], [0428], etc. for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP §608.01.

5. The use of trademarks has been noted in this application, e.g. Benzonase^{R}, TaqMan^{TM}, EasyComp^{TM}, etc., throughout the text. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objection

6. Claims 96 and 122 are objected to for following informalities: The term "a transdomain region" of Claim 96 should be "a transmembrane domain region". Claim 122 is objected to for depending from a withdrawn claim.

Claim Rejections - 35 USC § 101 Utility

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 94-98 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. "A polypeptide" comprising surface exposed fragment of SEQ ID NO:6042 of Claims 94-98 read on whole SARS S protein, which is a product of nature. Products of nature do not constitute patentable subject matter under 35 U.S.C. § 101. Amending the claims to "an isolated polypeptide" would overcome this rejection.

Claim Rejections - 35 USC § 112, first paragraph-Scope of Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 22, 23, 25-28, 114, 115 and 117 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a polypeptide comprising a SARS virus Spike (S) polypeptide, or a fragment thereof, does not reasonably provide enablement for use of such a polypeptide as a vaccine for treating or preventing of severe acute respiratory syndrome (SARS).

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech Inc. v. Novo Nordisk 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in In re Wands 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

11. Claims 22, 23, 25-28, 114, 115 and 117 are directed to a vaccine comprising SARS virus

Spike (S) polypeptide SEQ ID NO: 6042 or a fragment thereof for the treatment or prevention of severe acute respiratory syndrome (SARS). The scope of the claims encompasses prophylactic and therapeutic use of SARS S polypeptides, particularly S polypeptide of SARS Tor strain (S_{Tor2}), for treating or preventing SARS caused by any SARS-CoV in a subject, including humans.

12. In support the claims, the specification has disclosed how to make subunit S polypeptides, and has proposed immunogenicity studies of such S peptides in mice, rabbits and Ferrets (Examples 7-9), but no data have been presented. The specification has not shown whether or not the alleged vaccine comprising S polypeptide SEQ ID NO: 6042 or SEQ ID NO:7307 could induce protective immunity in any animal models against SARS infection caused by SARS tor2 strain, or other SARS-HcoV strains, nor whether not the alleged vaccine can be used for treating SARS infection. It is noted that the specification has disclosed that inactivated SARS virus can induce neutralizing antibodies in mice and Balb/c mice (Example 4 and 5). Example 5 shows that no SARS virus was detected in Balb/c mice immunized with inactivated SARS virus (Example 5). Although the specification has proposed more vaccine testing in animal models prior to human administration, including ferrets and monkeys (Para [0759]), no experiments have actually been performed.

13. However, the art indicates that mice model is not art-recognized animal model for assessing SARS infection. The art indicates that animal models to study the efficacy of SARS vaccines are not available (Weiss, Microbiol Mol Biol Rev. 2005; 69(4):635-64. Para 4, right col. p. 653). Although some animals, such as mice, hamsters, nonhuman primates or ferrets, are used for experimental testing, there are no animal models available for study of SARS because

none of the above mentioned animals reproduce the SARS-induced disease observed in humans

14. Furthermore, the art has indicated that the instant claimed invention is highly unpredictable because a vaccine for a new virus is not routinely achievable, and one of ordinary skill in the art was not in passession of knowledge of any vaccines or drugs for treating and preventing the newly emerged human SARS viruses at the time the instant invention was made. At the time the invention was made, a new class of human coronaviruses was just identified as the etiological agent of SARS. A few SARS-CoV strains, such as Tor2, Urbani, CHHK-W1 and HKU-39849 isolates, were just isolated and their genomes were just characterized (Marra, Science 300(5624):1399-404, 2003, cited in IDS; and Rota, Science 300:1394-1399, 2003, cited in IDS). However, the molecular biology and pathogenesis of SARS-HCoV were largely unknown. Importantly, the prior art indicates that no drug or treatment has been proven to be effective for control of SARS (Stockman 2006, PLoS Med 3(9):e343). No any vaccine against SARS was available. Thus, one of skill in the art was not in possession of knowledge of treating and preventing SARS at the time the alleged invention was made.

15. Because lacking knowledge of newly emerged new class of human coronaviruses, our knowledge of SARS vaccine development is largely based on other known animal coronaviruses (Cavanagh, Avian Pathol. 2003, 32(6):567-82). Howevr,the prior art shows that vaccines against avian infectious bronchitis coronavirus (IBV) cannot induce long-lasing and cross-protection in chickens. Cavanagh teaches that immunity induced by one IBV isolate protects poorly against infection by heterologous serotypes, although there are small differences in the amino acid sequences of S1 proteins (Cavanagh, p.571). Based the experience of IBV vaccine development, Cavanagh states that if SARS coronavirus were re-emerge in humans, its S1 protein might not be

the same as that the 2002/2003 outbreak. Research with IBV has indicated the differences of only 5% of S1 protein amino acid can reduce cross-protection (Para 5, right col. p. 577).

16. In view of these teachings, it is unpredictable in the art whether or not the alleged vaccine comprising comprising S_{Tor2} peptides could protect or inhibit other strains of SARS-HCoV, thus treating or preventing all SARS-HCoV infections in a subject as claimed. It would require extensive research to develop a vaccine for treating and preventing SARS-CoV infections. Considering the state of the art, and in view of the empirical and unpredictable nature of the art of virology, and lack of working examples with respect to assessment of alleged vaccines comprising SARS S polypeptides, one skilled in the art would have to do an **undue** amount of experimentation to develop an SARS vaccine comprising S polypeptides for treating and preventing SARS in a subject. Therefore, the specification, at the time the application was filed, the specification does not enable one skilled in the art to use the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 1-8, 22, 23, 27, 28, and 94 are rejected under 35 U.S.C. 102(e) as being

anticipated by Plummer (US20070258999, Provisional application 60/465783, Effective filing date April 28, 2003), as evidenced by Dimitrov (US2006/0240515A1, provisional application No. 60/489,166 filed on July 21, 2003).

19. Claims 1-8, 22, 23, 27, 28, 94 and 122 read on an isolated polypeptide, or a vaccine, **comprising** a SARS coronavirus Spike (S) polypeptide SEQ ID NO:6042, or a fragment S1 SEQ ID NO:7307, wherein the polypeptide is in oligomeric form, wherein the oligomer is a trimer, wherein the polypeptide comprising an immunogenic, surface-exposed fragment of the amino acid sequence SEQ ID NO: 6042, wherein the polypeptide is a fusion peptide comprising S protein SEQ ID NO: 6042.

20. Plummer teaches a S polypeptide of SARS coronavirus Tor2 strain (S_{Tor2}) shown as SEQ ID NO: 33 (See [0056] and Figure 5), The S_{Tor2} SEQ ID NO:33 is 100% identical to the claimed polypeptide SEQ ID NO: 6042, as evidenced by the attached sequence alignment. S_{Tor2} polypeptide is a fusion polypeptide comprising a S1 domain and a S2 domain, of which S1 domain has a amino acid sequence 100% identical the claimed S1 fragment SEQ ID NO:7307. Plummer teaches that S_{Tor2} glycoprotein SEQ ID NO:33 belongs to a type I membrane protein with N-terminus and the majority of the protein (residues 14-1193) are on the outside of the cell-surface or virus particle, which may be responsible for binding to a cellular receptor (Para [0084]). Thus, Plummer teaches that S_{Tor2} SEQ ID NO:33 comprises a surface-exposed fragment of the claimed amino acid sequence SEQ ID NO: 6042.

21. Although Plummer does not explicitly teach that S polypeptide is a trimer (claim 5), S polypeptide can form a trimer, as evidenced by Dimitrov. Dimitrov teaches that like viral envelope glycoproteins of class I fusion proteins, the full-length membrane-associated S

polypeptide and some soluble peptides thereof are trimeric through the transmembrane domain (Para [0204] and [0207]).

22. Plummer teaches that a SARS virus Spike polypeptide may be suitable for vaccine applications, and the vaccines may be multivalent and include one or more epitopes from a SARS virus polypeptide or fragment thereof (Para [0110]). In view of these teachings, Claims 1-8, 22, 23, 27, 28, 94 and 122 are anticipated by Plummer.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 95-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plummer (US20070258999), as applied to Claim 94 above, in view of Cavanagh D et al (J Gen Virol. 1986 Jul;67:1435-42).

25. Claims 95-98 are directed to the polypeptide of Claim 94, wherein said fragment does not include the last 50 amino acids of the *C*-terminus of SEQ ID NO: 6042, wherein said fragment does not include a transdomain region of SEQ ID NO: 6042, wherein said fragment does not include a *C*-terminus cytoplasmic domain of SEQ ID NO: 6042, and wherein said fragment does not include a *N*-terminus signal sequence.

26. The relevance of Plummer is set forth *supra*. Moreover, Plummer teaches that SEQ ID NO: 33 contains a signal peptide (MFIFLLFLTLTSG; SEQ ID NO: 76) from amino acids 1-13 at its *N*-terminus, and a transmembrane domain WYVWLGFIAGLIAIVMVTILLCC from amino acids 1194 to 1216, which is about 60 amino acids of the *C*-terminal end of S_{Tor2} SEQ ID NO:33. Plummer teaches that residues 14-1193 of S_{Tor2} SEQ ID NO:33 are on the outside of the cell-surface or virus particle, which may be responsible for binding to a cellular receptor (Para [0084]).

27. Plummer does not explicitly teach making S_{Tor2} peptide fragments lacking an *N*-signal peptide and/or a *C*-terminal transmembrane domain.

28. Cavanagh teaches that the S1 subunit of IBV spike protein, which lacks a *C*-terminal transmembrane domain (S2 subunit), is the major inducer of virus neutralizing antibodies (Whole document, particularly p.1440-1442). Cavanagh teaches that vaccination of chickens with the S1 subunit alone was able to induce virus-neutralizing antibodies, but virus that lacked the S1 subunit was unable to induce neutralizing antibody (Title, pp. 1439-1442).

29. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make S_{Tor2} peptide fragments lacking an *N*-signal peptide and/or a *C*-terminal transmembrane domain as a vaccine component. One skilled in the art would have been motivated to generate the claimed S_{Tor2} peptide fragments, and has a reasonable expectation of success that such fragments are immunogenic and can induce neutralizing antibodies, given the knowledge that the surface-exposed fragment of SEQ ID NO: 6042, but not an *N*-signal peptide and the *C*-terminal 50 amino acids of SEQ ID NO: 6042 containing the transmembrane domain, is responsible for receptor binding and induction of neutralizing antibodies, as taught by

Plummer and Cavanagh. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

30. Claims 25, 26, 114, 115 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plummer (US 20070258999), as applied to Claim 22 above, in view of Gasparini *et al*. (European Journal of Epideminology 17:135-140, 2001).

31. Claims 25, 26, 114 and 115 are directed to a vaccine of Claim 22 further comprising an adjuvant, wherein the adjuvant is MF59. Claim 117 is directed to a method of vaccinating a subject comprising administering to the subject a vaccine of Claim 22.

32. The relevance of Plummer is set forth *supra*.

33. Plummer does not teach use of either MF59 as a vaccine adjuvant, or a method of vaccinating a subject using the S peptide of Claim 22.

34. Gasparini teaches a method of vaccinating a subject using the MF59-adjuvanted influenza subunit vaccine comprising surface antigens of influenza virus (entire document, particularly Abstract). Gasparini teaches that a subunit influenza vaccine with adjuvant MF59 is more immunogenic. Statistical analysis showed that more subjects developed enhanced immunogenicity to SARS CoV who received subunit influenza vaccine with adjuvant MF59 than those who received conventional subunit influenza antigens without MF59 (p. 137).

35. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use an adjuvant like MF59 with alleged SARS S peptide vaccine for the purpose of enhancing the immunogenicity of the alleged subunit vaccine. One skilled in the art

would have been motivated to generate the claimed invention with a reasonable expectation of success, given the knowledge that vaccine adjuvant, like MF59, can enhance immunogenicity of subunit peptide antigens, as taught by Gasparini. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Remarks

36. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
Patent Examiner
August 20, 2008